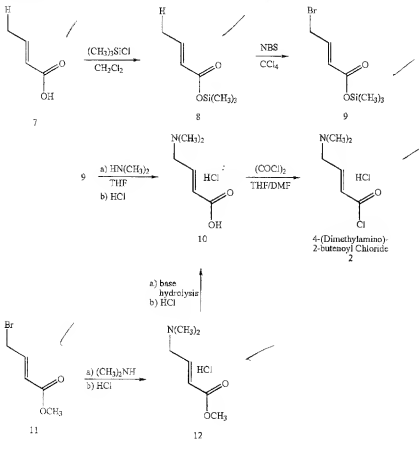
ERROR (#)

isolated as the hydrochloride salt. Alternatively, 4-dimethylaminocrotonic acid 10 can be prepared by reaction of methyl or ethyl 4-bromocrotonate 11 with dimethylamine at 0 to 10° C. in tetrahydrofuran to give methyl or ethyl 4-dimethylaminocrotonate 12 which is hydrolyzed with aqueous base which includes sodium hydroxide in methanol as a cosolvent at about 40–45° C. to give 4-dimethylaminocrotonic acid 10 which is isolated to 4-dimethylaminocrotonic acid (hydrochloride) 10 with a solution of hydrogen chloride in isopropyl alcohol, and then chlorinated with a chlorinating agent preferably, but not limited to, oxalyl chloride in methylene chloride, tetrahydrofuran (THF) or acetonitrile in the presence of a catalytic amount of N,N-dimethylformamide to afford 4-(dimethylamino)-2-butenoyl chloride hydrochloride 2.

SCHEME II:



Trimethylsilylcrotonate

Pyridine (138 g, 1.74 mol) is added dropwise to a stirred solution of crotonic acid (125 g, 1.45 mol), and chlorotrimethylsilane (189 g 1.74 mol) in ether (1.5 l) at room temperature. The reaction mixture is allowed to stir at room temperature overnight and the precipitate is removed by filtration. The filtrate is concentrated and the residue is distilled under reduced pressure. The product fraction is collected at 58–70° C. (25 mmHg) to give 180 g of the title compound (79%). GC-MS purity is 93.4%, ^{1}HNMR is consistent with the structure.

Trimethylsilyl-4-bromocrotonate

A stirred mixture of trimethylsilylcrotonate (131 g, 0.828 mol), N-bromosuccinimide (206 g, 1.16 mol), benzoyl peroxide (3.41 g, 0.141 mol) and carbon tetrachloride (1 L) is warmed to reflux (77° C.) under visible light for 5 hours. The mixture is cooled to room temperature and the precipitated solid is removed by filtration. The filtrate is concentrated to a residue, which is distilled under reduced pressure. The product fractions are collected at 93–106° C. (9–15 mmHg) to give 127 g of the title compound (65%). GC-MS purity is 83–89%, ^{1}HNMR is consistent with expected structure.

4-Dimethylaminocrotonic acid

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A solution of 211 ml of dimethylamine (2M in tetrahydrofuran, 0.422 moles) is added dropwise to a solution of 50 g trimethylsilyl-4-bromocrotonate (0.211 moles, 75.9% by GC-MS) in 250 ml of tetrahydrofuran at 0–5° C. under N_2. The reaction mixture is stirred at room temperature for 30 minutes. A white solid by-product is removed by filtering and 2 ml water is added to the filtrate followed by seeding.

ERROR (7)

Trimethylsilylcrotonate

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4-Dimethylaminocrotonic acid

A solution of 211 ml of dimethylamine (2M in tetrahydrofuran, 0.422 moles) is added dropwise to a solution of 50 g trimethylsilyl-4-bromocrotonate (0.211 moles, 75.9% by GC-MS) in 250 ml of tetrahydrofuran at 0-5° C under N_2. The reaction mixture is stirred at room temperature for 30 minutes. A white solid by-product is removed by filtering and 2 ml water is added to the filtrate followed by seeding. The crystals formed are filtered and washed with ether to give 18.3 g (from two crops) of the desired product as off-white solid. Yield is 67.2% (98% purity by GC-MS, NMR is consistent with the expected structure).